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SPECIAL ISSUE

New directions in clinical trials for frontotemporal lobar degeneration: Methods and outcome measures

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Abstract

Introduction: Frontotemporal lobar degeneration (FTLD) is the most common form of dementia for those under 60 years of age. Increasing numbers of therapeutics targeting FTLD syndromes are being developed.

Methods: In March 2018, the Association for Frontotemporal Degeneration convened the Frontotemporal Degeneration Study Group meeting in Washington, DC, to discuss advances in the clinical science of FTLD.

Results: Challenges exist for conducting clinical trials in FTLD. Two of the greatest challenges are (1) the heterogeneity of FTLD syndromes leading to difficulties in efficiently measuring treatment effects and (2) the rarity of FTLD disorders leading to recruitment challenges.

Discussion: New personalized endpoints that are clinically meaningful to individuals and their families should be developed. Personalized approaches to analyzing MRI data, development of new fluid biomarkers and wearable technologies will help to improve the power to detect treatment effects in FTLD clinical trials and enable new, clinical trial designs, possibly leveraged from the experience of oncology trials. A computational visualization and analysis platform that can support novel analyses of combined clinical, genetic, imaging, biomarker data with other novel modalities will be critical to the success of these endeavors.

KEYWORDS

ARTFL, Biomarker, C9orf72, Clinical trial, Frontotemporal dementia, Frontotemporal lobar degeneration, FTD, FTLD, GRN, LEFFTDS, MAPT, Primary progressive aphasia, Progressive supranuclear palsy

1 | INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is the neuropathological term for a related group of rare neurodegenerative disorders that cause a spectrum of impairments in personality, cognitive ability, language, and motor function. These include behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasias (PPA) and the parkinsonian disorders, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). At present, there are no approved symptomatic or disease-modifying treatments for FTLD. Medications that are approved for use in other diseases are often used to manage FTLD symptoms without lasting success, and none have been found to slow or stop the progression of FTD.[1–3] Current management for FTLD relies on these symptomatic therapies as well as nonpharmacological interventions that include reduction of excess stimulation from the environment combined with management of inappropriate or repetitive behaviors using tailored activity programs[4,5] and language retraining or speech therapy where possible.[6,7] The use of physiotherapy and occupational therapy and modifications to the home environment can support progressive loss of motor skills.[8] These interventions offer partial but temporary symptomatic relief and address some of the caregiver burden but do not substantially alter the course of this fatal spectrum of disease. Later disease stages often require institutional care where behavioral problems, mutism, parkinsonism, and dysphagia are managed symptomatically.

The Frontotemporal Degeneration Treatment Study Group (FTSG), a program of the Association for Frontotemporal Degeneration, was founded in 2010 to promote collaborations between academic and pharmaceutical industry researchers focused on drug development for FTLD and related disorders.[2,9] Since the last FTSG meeting that took place in 2016, much progress has been made in therapeutically relevant FTLD research. With increasing numbers of potential therapies entering familial FTLD (f-FTLD) clinical trials, the FTSG organized a meeting in Washington, DC, March 2018, in partnership with the National Institute of Neurological Disorders and Stroke, to discuss clinical trial methodology and outcome measures for the FTLD spectrum of disorders. Two key challenges to FTLD clinical trial design were identified as topics for this meeting: (1) the heterogeneity of clinical symptoms in FTLD syndromes caused by the same mutation or underlying pathology, leading to difficulties in efficiently measuring treatment effects using clinical or imaging outcome measures; and (2) the rarity of FTLD disorders leading to recruitment challenges and the necessity for trial designs and instruments that can optimize the measurement of treatment effects in small trial samples. This article summarizes the presentations and discussion from that meeting and highlights new strategies to improve FTLD drug development.

2 | CLINICAL TRIAL DESIGN IN RARE FTLD DISORDERS

The complexity of FTLD phenotypes and range of syndromes creates a significant challenge for clinical trial design, along with the fact that the FTLD disorders are considered rare diseases (less than 200,000 affected in the US). Collecting true population-based estimates for FTLD disorders is problematic given the limited public awareness of this younger onset dementia, clinical presentations that can overlap with other diseases, and the absence of validated biomarkers to distinguish FTLD from other neurological and psychiatric disorders. A recent study in the UK[10] reported a combined prevalence of 10.8 per 100,000 for bvFTD, PPA, PSP, and CBS for all ages (40–100 years) with a peak between 65 and 70 years of approximately 45 per 100,000 which is consistent with previous prevalence estimates for FTD and PPA.[11,12] Interest in participation in clinical trials is very high among f-FTLD kindreds as well as families living with sporadic FTLD, which has facilitated a number of multisite clinical trials for FTLD disorders including bvFTD, semantic variant PPA, and multiple studies in PSP.[13–16] Greater than 85% of participants in a survey for the Advancing Research and Therapies in Frontotemporal Lobar Degeneration (ARTFL) North American clinical research consortium, described in the following, indicated a strong interest to participate in a clinical trial.

There have been few randomized, placebo-controlled trials in FTLD.[3] Previous clinical trials have demonstrated the feasibility of using behavioral questionnaires, cognitive scales, and functional activity ratings as outcome measures. Although no study to date has yielded evidence of disease modifying therapeutic efficacy, previous trials have laid the groundwork for sharing data that could improve trial design.[17] Previous trials may have been unable to detect treatment effects for a number of reasons such as outcome measures that do not address clinical, etiological, and imaging heterogeneity between patients carrying the same molecular diagnosis, inadequate sample size, and participants being too late in the course of the disease to demonstrate benefit. Refining FTLD patient selection and trial design will gain even greater importance as new disease-modifying therapeutics are developed.[17] The two largest industry-sponsored trials in bvFTD (NCT01626378) and FTLD due to progranulin gene mutations (FTLD-*GRN*; NCT02149160) have not yet been published, and it is anticipated that data shared from these studies would advance our understanding of trial design for FTLD. Stronger mechanisms to ensure prompt publication and data sharing, based on the Collaboration for Alzheimer's Prevention principles,[18] will be particularly important for a rare disease and need to be incorporated into future FTLD clinical trials.

Despite these challenges, new treatments targeting tau gain of function, progranulin haploinsufficiency, and chromosome 9 open reading frame 72 (*C9orf72*) hexanucleotide repeat expansions are progressing in clinical development for FTLD and related disorders, with some agents such as anti-tau monoclonal antibodies having entered large-scale efficacy studies for PSP (NCT02460094 and NCT02985879). Table 1 summarizes drugs recently tested, in late stages of preclinical development, or currently under active evaluation in clinical trials.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources, meeting abstracts and presentations. There have been a limited number of randomized placebo-controlled clinical trials performed in frontotemporal lobar degeneration syndromes in the past. A variety of endpoints have been used in these studies; all were negative. The relevant citations are appropriately cited.
2. Interpretation: A variety of challenges exist for conducting clinical trials in frontotemporal lobar degeneration (FTLD). Most prominently, these are 1) the heterogeneity of FTLD syndromes leading to difficulties in efficiently measuring treatment effects using common clinical or imaging outcome measures and 2) the rarity of FTLD disorders leading to recruitment challenges and difficulties with adequate power to detect treatment effects.
3. Future directions: A limited number of clinical trials are underway and more are planned for both familial and sporadic FTLD syndromes. New personalized endpoints that are most clinically meaningful to individuals and their families should be developed. In addition, more powerful approaches to analyzing heterogeneous clinical and MR imaging data and development of new fluid biomarkers and wearable technologies will help to improve the power to detect treatment effects in FTLD clinical trials and enable new, more efficient clinical trial designs modeled on oncology. More widespread sharing of clinical trial data and biofluid samples will be critical to developing new endpoints and refining FTLD clinical trial designs.

These ongoing and planned clinical trials across the spectrum of FTLD highlight the urgency of developing novel outcome measures, patient stratification tools and clinical trial designs. Therapies that leverage or modify the immune system to treat FTLD are now in clinical trials. Tau immunotherapies are being tested by several groups who are leveraging the clinical homogeneity of patients with PSP-Richardson's syndrome[16,39] or nonfluent variant PPA,[40] which are considered "pure" 4 repeat tauopathies with well-defined natural history of disease progression. These FTLD syndromes provide cohorts in whom it may be easier to demonstrate, and hopefully define, clinically meaningful endpoints that could achieve regulatory approval. A trial of a monoclonal antibody that blocks a progranulin receptor, and thereby hypothesized to increase progranulin levels, is also now underway (Table 1).

Antisense oligonucleotide (ASO) therapy has been demonstrated to be effective in the central nervous system when used to treat spinal muscular atrophy.[41,42] Oligonucleotides offer the opportunity for precision design with a sequence and modifications that can improve their selectivity, stability, and specificity. Current platforms create either a

TABLE 1 Potential FTLD therapeutics

Drug	Mode of action	Status	Ref	NCT*
GRN-targeted therapeutics				
FRM-0334	HDAC inhibitor	Phase 2 (negative)	n/a	01835665
Chloroquine	Vesicular pH modulator	Repurposed	[19]	-
Nimodipine	Increased progranulin secretion	Repurposed; phase 1b (neg)	[20]	01835665
AL-001	Anti-sortilin mAb	Phase 1	n/a	03636204
Proprietary A, B	HDAC inhibitor	Preclinical	[21]	-
Proprietary A-C	AAV gene therapy	Preclinical	[22,23]	-
C9orf72 therapeutics:				
Proprietary A, B	*C9orf72* antisense oligonucleotides	Phase 1 ALS; FTLD planned	[24,25]	03626012
Tau-targeted therapeutics:				
LMTX (methylene blue)	Protein clearance activator	Phase 3 (negative for bvFTD)	n/a	01626378
Lithium carbonate	GSK inhibitor	Phase 2 FTD	n/a	02862210
Abeotaxane (TPI-287)	microtubule stabilizer	Phase I (negative for CBD, PSP)	n/a	01966666
Salsalate	Tau acetylation inhibitor	Phase 1 PSP; abandoned	[26]	02422485
ABBV-8E12	N-terminal anti-tau mAb	Phase 2 PSP (abandoned)	[27]	02985879
BIIB092	N-terminal anti-tau mAb	Phase 2 PSP	[28]	02460094
BIIB092	N-terminal anti-tau mAb	Phase 1b: CBD, nfvPPA, s*MAPT*	[28]	03658135
AADvac1	Active anti-tau vaccine	Phase 1: nfvPPA	[29]	03174886
UCB0107	Mid-domain anti-tau mAb	Phase 1	[30]	-
ASN001	o-GlcNACase inhibitor	Phase 1	[31]	-
IONIS-*MAPT*rx	Antisense oligonucleotide	Phase 1 AD	[32]	03186989
Other (immunomodulatory, neuroprotective therapeutics):				
NP001	Macrophage activation inhibitor	Phase 2 ALS (negative)	[33,34]	03186989
DLZ Kinase inhibitor	Neuroprotective agent	Phase 1 ALS	[35]	02655614
Symptomatic approaches:				
Oxytocin	Symptomatic improvement	Phase 2 bvFTD	[36]	01386333
Rivastigmine	Cholinesterase inhibitor	Phase 2 PSP	n/a	02839642
Transcranial DC stim	Electric current stimulation	N/A (pilot) bvFTD, PPA	[37]	02999282
Transcranial magn. stim	Magnetic field stimulation	PPA	[38]	03406429

Abbreviations: *C9orf72*, chromosome 9 open reading frame 72; FTLD, frontotemporal lobar degeneration; PPA, primary progressive aphasias; bvFTD, behavioral variant frontotemporal dementia; ALS, amyotrophic lateral sclerosis; PSP, progressive supranuclear palsy; AD, Alzheimer's disease; nfvPPA, non-fluent variant Primary Progressive Aphasia.
*NCT, www.clinicaltrials.gov registration number.

stereo-random mixture of oligonucleotides, or more recently a pure stereo-isomer.[42] Two different ASO programs targeting the *C9orf72* mutation are approaching the clinical stage for FTLD and an anti-*MAPT* ASO trial is underway in Alzheimer's disease (AD). This ASO could also potentially be used to treat FTLD due to *MAPT* mutations or PSP in the future.

Studies of FTLD syndromes using clinical endpoints and volumetric MRI provide a measure of disease progression and indicate that many FTLD syndromes (bvFTD, CBS, PSP) progress more rapidly than AD thereby enabling smaller and shorter trials and the potential to learn from successes and failures more quickly.[43] Clinical trials that enroll presymptomatic familial FTLD (f-FTLD) mutation carriers have the potential to act as disease "prevention" studies, but will be more dependent on the development of biomarkers that are highly predictive of clinical outcomes in a reasonable period following treatment. Following the model of the Dominantly Inherited Alzheimer's Network Treatment Unit trials,[44,45] FTLD natural history studies are beginning to develop similar capabilities.

3 | THE ROLE OF NATURAL HISTORY STUDIES IN FTLD

In 2013, the National Alzheimer's Project Act–Alzheimer's Disease-Related Dementias Summit identified key research priorities for FTLD.[46] With an ultimate goal of developing effective therapies for FTLD, the clinical research priorities included the formation of a clinical trials ready research network and development of new biomarkers for FTLD. The ARTFL network, created in 2014, is a large cross-sectional and natural history study of sporadic and familial FTLD disorders in

the US and Canada. Fully integrated with this program is the Longitudinal Evaluation of Frontotemporal Dementia Subjects (LEFFTDS) project, a detailed, longitudinal observational study of autosomal dominant FTLD-causing mutation families (*C9orf72*, *GRN*, or *MAPT*), with a focus on developing presymptomatic biomarkers for FTLD.[47]

Like the LEFFTDS network, the Genetic Frontotemporal Dementia Initiative (GENFI) network also follows f-FTLD kindreds with a goal of developing multimodal MRI and fluid biomarkers and genomics methods to identify predictive factors, neuroanatomic correlates, and variability in the natural history of disease progression.[39,48,49] By focusing on asymptomatic or mildly symptomatic f-FTLD patients who have relatively little neuropathology, future clinical trials should have improved power to detect treatment effects of new therapies.

More robust natural history data from all FTLD syndromes is needed to develop clinically meaningful outcome measures and to better inform drug development for both symptomatic and disease-modifying therapies. Functional and quality of life outcomes may provide opportunities to capture clinically meaningful outcome measures for a broad variety of FTLD phenotypes, but there are few such outcome measures at this time that are FTLD-specific. A better understanding of how persons diagnosed with FTLD and their caregivers would define meaningful functional stabilization or improvements that impact quality of life is needed.[50,51] In addition, what constitutes a clinically meaningful benefit for asymptomatic or questionably symptomatic mutation carriers is not agreed on.

4 | HETEROGENEITY OF FTLD SYNDROMES AND OUTCOME MEASURES: NEW APPROACHES TO MEASURING DISEASE PROGRESSION

FTLD encompasses an array of clinical syndromes involving behavior, speech, and/or motor deficits that arise from a handful of similar underlying brain pathologies, most commonly FTLD-tau or FTLD-TDP.[52,53] The clinical course of FTLD generally begins as one of the distinct phenotypic variants and often progresses to involve other cognitive, behavioral, and motor domains.[54] Survival ranges from 2 to 13 years after diagnosis (depending on clinical syndrome and underlying pathology), but averages about 8–10 years.[55] Slower progression cases with longer survival (ranging 20–30 years) have been described.[56,57] Existing clinical instruments such as the Neuropsychiatric Inventory may help classify subtypes within a particular syndromic diagnosis such as behavioral variant FTD[58] but cannot identify the underlying molecular pathology causing the syndrome.[59] Volumetric MRI is currently the best available technology at an individual level for the *in vivo* identification of neuron loss in FTLD, although the neuropathological correlates of MRI defined brain atrophy have not been fully validated.[60] Resting-state fMRI can identify abnormalities in presymptomatic mutation carriers[61] but FDG PET may be more promising for capturing disease progression.[62] Emerging data demonstrate the correlation of bvFTD subtypes with distinct patterns of degeneration[63,64] and provide a potential network-based model of the various phenotypes.[65] Furthermore, data-driven approaches applied to volumetric MRI from genetic FTLD also shows promise for identifying different FTLD syndromes.[66,67] MRI-based imaging measures such as voxel-based morphometry, diffusion tensor imaging, and arterial spin label perfusion change over time in individual FTLD patients and generally show good correlations with clinical measures.[68] A challenge is that the data acquired from these images are often highly variable across syndromes caused by the same underlying pathology, but also even within the same clinical FTLD syndrome. Ideally an imaging method would provide a way of following an individual patient's atrophy patterns regardless of FTLD syndrome to predict or distinguish their variable trajectory.

4.1 | MRI-based approaches to account for heterogeneity within FTLD syndromes

The underlying phenotypic heterogeneity of FTLD clinical syndromes argues for a personalized medicine approach able to capture individualized measures of change based on the patient's baseline phenotype. A new imaging approach being investigated is the use of W-score maps that highlight how each individual voxel's W-score (similar to Z-score, corrected for demographic variables) in FTLD images differ from those in normal brains, allowing quantification of the total burden or pattern of atrophy and assigning scores based on these maps which clearly differentiate CDR® Dementia Staging Instrument plus NACC FTLD Behavior & Language Domains (CDR® plus NACC FTLD) = 0 (asymptomatic) from CDR® plus NACC FTLD = 1 (fully symptomatic) or higher.[67,69] These maps may aid in the visualization of early neurodegenerative change; however, more data sets from younger healthy controls will be required to understand the observed variations in the rate of change. Increasingly, MR imaging is being combined with putative fluid biomarkers in an effort to stage and monitor FTLD with prediction of progression through a multimodal approach.[70–72]

4.2 | A new, multidomain, global rating scale to measure clinical heterogeneity

The LEFFTDS and ARTFL networks have developed a new scale based on the FTLD-CDR[69] that incorporates motor and sensory domains as well as separate streams of information for patients, informants, and neuropsychologists, called the Multidomain Impairment Rating (MIR) scale as a global and quantitative clinical burden rating scale (Boeve et al., personal communication). The MIR is designed to be more sensitive than standard scales to the earliest signs and symptoms of FTLD in mutation carriers. Using standard lobar volumetric assessments, volumetric MRI in *MAPT* and other f-FTLD kindreds demonstrate prominent atrophy rates in symptomatic carriers, intermediate rates in asymptomatic carriers, and only age-related changes in noncarriers.[73] Modeling such rates of decline across different imaging modalities in mutation carriers at different MIR-defined stages of disease may help to understand phenoconversion from clinically

TABLE 2 Draft FDA guidance for approvals in presymptomatic/early AD

	Stage 1	Stage 2	Stage 3	Stage 4
	Preclinical	**Prodromal (MCI)**	**Early AD**	**Mild-moderate AD**
Definition	• Asymptomatic • Biomarker evidence of pathology (only)	• Detectable cognitive changes • No functional impairment	• Cognitive impairment • Mild functional impairment	• Overt dementia • Cognitive and functional impairment
Possible endpoints	• Biomarker • Imaging	Cognitive scale(s) only (biomarker supported dx)	Clinical scale(s) to assess both daily function *and* cognitive effects	Clinical scale(s) to assess both daily function *and* cognitive effects
Clinically meaningful effect for approval?	Not required	Clinically meaningful ideal; *not required*	Clinically meaningful effect required	Clinically meaningful effect required

asymptomatic to symptomatic FTLD. A better understanding of the onset, duration, and variability of this window could also lead to the identification of biomarkers that can predict or measure this change. The MIR will likely be an important tool to timestamp phenoconversion, a necessary step in biomarker validation.

4.3 | Fluid biomarkers

There is a growing literature on cerebrospinal fluid (CSF) and blood neurofilament light chain (NfL), viewed as a biomarker of neurodegeneration[74–76] and as a candidate marker of disease onset in FTLD. Furthermore, it may serve as a prognostic biomarker for genetic and sporadic FTLD[77–79] and reflect disease severity and rate of progression in some sporadic FTLD subtypes.[75,80–82] Recent biomarker development studies reflect a growing trend to create test panels with a combination of a large number of analytes to discriminate between clinically defined syndromes within FTLD and other neurodegenerative diseases such as AD and amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) disorders.[77] However, a weakness of this approach is that many previous efforts using statistically clustered combinations of fluid biomarkers have failed to replicate. Other potential fluid biomarkers that reflect changes in autophagy, neuroinflammation, RNA metabolism, and mitochondrial function are a growing area of study in FTLD and other dementias;[85] however, it is not well understood whether this broader spectrum of measures will reflect early neurodegenerative processes or late responses to neurodegeneration.

Relating these biomarkers to the accumulation of insoluble deposits of tau and/or TDP-43 measured at autopsy in FTLD will be important. Even the relationship of TDP-43 and tau deposition to the onset and progression of sporadic FTLD syndromes is not well understood. For example, other than in *MAPT* or *TARDBP* mutation carriers, it is not known whether changes in these proteins initiate, mediate, contribute to, or simply reflect other processes that drive disease progression. The complexity of biomarker discovery and validation for various heterogeneous FTLD syndromes in comparison with the simpler and more pathologically and clinically homogeneous AD syndromes has resulted in fewer FTLD specific biomarkers, and as yet no presymptomatic biomarkers of sporadic disease. This makes it more challenging to develop a biological definition for FTLD, as has been recently suggested for AD.[86] Similarly, applying the recent FDA draft guidance for prodromal AD drug development (Table 2) allowing for accelerated approvals based on fluid or imaging biomarkers[87] represents a higher hurdle for prodromal FTLD. Nevertheless, with the strong data already obtained using CSF and blood NfL, use of this fluid biomarker to define or predict onset of clinical symptoms may enable FTLD prevention trials in asymptomatic or early symptomatic FTLD mutation carriers. In such a scenario, the time to elevation in blood NfL or the rate of increase of NfL concentration in the late presymptomatic stage of disease or even change from the baseline could be used as potential endpoints for prevention trials (Table 2). Such a scenario will require that blood NfL levels strongly correlate with underlying neurodegeneration and are strongly predictive of future clinical status allowing them to be validated as a surrogate endpoints as has been done in other diseases such as HIV or cancer, in which some clinical trials have relied on a surrogate biomarkers that predicts future disease for approvals.[88]

5 | AUTOSOMAL DOMINANT FTLD AND SPORADIC FTLD—THE SAME DISEASE?

The autosomal dominant FTLD gene mutations afford a unique insight into the molecular "switches" that convert asymptomatic to symptomatic mutation carriers. It is hoped that the biology of this prodromal transition will also provide new insight into the causes and earliest biological changes in sporadic FTLD. Although the autosomal dominant gene mutations provide greater confidence for an FTLD diagnosis and can help to assure recruitment of the right patients into clinical trials, it is not clear how different FTLD-causing mutations lead to biochemical changes that converge on the same brain networks that produce the unique phenotypes associated with FTLD. Furthermore, while insights based on the study of f-FTLD are often relied on for drug discovery, it is not known how such genetic FTLD syndromes relate to sporadic FTLD or how findings developed in preclinical models based on a particular f-FTLD mutation (such as P301S *MAPT*) will relate to other genetic (such as V337M *MAPT*) FTLD patients. Initial data from bvFTD patients carrying mutations in *C9orf72*, *GRN*, or *MAPT* suggest that they are very similar from a clinical and MR imaging perspective to sporadic FTLD patients (Heuer et al., in press at *Alzheimer's & Dementia*).

TABLE 3 Application of draft early AD approval guidance to FTLD

	Stage 1	Stage 2	Stage 3	Stage 4
Population	Preclinical (mut. carriers)	Prodromal (MCI/MBI)	Early dementia	Mild-moderate disease
FTLD-CDR	FTLD-CDR = 0	FTLD-CDR = 0.5	FTLD-CDR = 1.0	FTLD-CDR > 1.0
Definition	• Asymptomatic • Biomarker evidence of pathology (only)	• Questionable or mild clinical disease • No functional impairment	• Clinical impairments • Mild functional impairment	• Overt dementia • Clinical or functional impairment
Possible endpoints	Biomarker • NfL Imaging • regional brain atrophy	Clinical scale ± Biomarker	Clinical scale(s) to assess both daily function *and* clinical effects	Clinical scale(s) to assess both daily function *and* cognitive effects
Clinically meaningful effect for approval?	Not required	Clinically meaningful ideal; *not required*	Clinically meaningful	Clinically meaningful

Abbreviations: AD, Alzheimer's disease; NfL, neurofilament light chain; FTLD, frontotemporal lobar degeneration; FTLD-CDR, CDR® Dementia Staging Instrument PLUS NACC FTLD Behavior & Language Domains; MCI/MBI, mild cognitive impairment/mild behavioral impairment.

An important question is when (and where) neurodegeneration in FTLD begins? In autosomal dominant FTLD, mutations are present from conception[89] and recent data in *C9orf72* mutation carriers suggest there is a lifelong propensity to develop psychiatric disorders. Furthermore, each gene demonstrates heterogeneity in its associated clinical syndromes, and family members with the same mutation may present with a different clinical syndrome[90] (M. Ramos et al., personal communication). *MAPT* mutations most often lead to a bvFTD phenotype, but may be expressed as the movement disorder syndromes of PSP or CBS. With more than 60 mutations and a small number of affected families, trying to map the different *MAPT* mutations to different brain networks is daunting.[91,92] *GRN* and *C9orf72* mutations offer similar challenges with *C9orf72* providing additional variability with of a mix of clinical syndromes that may be bvFTD, or ALS, or FTD with ALS, or ALS with a range of behavioral or cognitive impairment or with CBS or nonfluent variant PPA.[93–95] To best understand these processes, combining data from genetic and sporadic FTLD patients may be necessary. For example, a recent publication examined the overlap between ALS and FTLD revealing a number of novel loci and functional pathways shared by ALS, bvFTD, and PSP and that the *MAPT* H1 haplotype conferred risk for ALS.[96] Together, these studies suggest that studying both autosomal dominant and sporadic FTLD syndromes in parallel, with the same clinical, imaging, and biomarker tools, will help to overcome limitations of studying one population on its own, thereby increasing the likelihood of progress toward an effective therapy.

6 | DEVELOPING TARGETED THERAPIES FOR MOLECULARLY DEFINED SUBSETS OF A DISEASE

The FDA has recently issued draft guidance on "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease".[97] This guidance was issued to address challenges in the development of targeted therapies for diseases with multiple molecular subsets, when some of these subsets are too small to deliver robust and conclusive data. For these targeted therapies, moving forward with drug development toward approval is challenged by patient recruitment, interpretation of results and extrapolating findings to putatively similar molecular subtypes.[97] The new guidance recommends that grouping patients with different molecular alterations into a single trial may be based on a scientific rationale that the grouped patients will have a similar pharmacological response to a new drug. This would allow for the possibility of extrapolating efficacy findings across multiple subsets in spite of a low number of patients in some subsets. Although the guidance is focused on developing targeted therapies in low-frequency subsets within a single disease, some principles may be applicable to basket trial designs where more than one disease is included in a single clinical trial.[98] One such basket design clinical trial is now underway with an anti-tau monoclonal antibody in FTLD-tau syndromes (NCT03658135) and other similar studies in FTLD-TDP syndromes are planned.

Precision medicine has advanced in oncology by classifying many cancers by the presence of known pathogenic gene mutations, allowing for inclusion of additional patients in trials based on the presence of a specific genetic marker in their cancerous cells.[99,100] This ability to identify subpopulations that may respond to a specific treatment, and tailor treatment to the individual characteristics of each patient based on biomarkers, has contributed to an understanding of trial design elements that could also be applied to FTLD. In oncology, platform trials using master protocols with multiplexed biomarkers improve the efficiency of testing novel agents and allow for the use of common controls, thereby reducing overall sample sizes necessary to test multiple new drugs. Adaptive trials use the accumulating data to support decision-making on modifying a study in a prespecified manner such as dropping arms, using surrogate endpoints or adaptive randomization and Bayesian analysis.[101,102] For example, therapeutics for glioblastoma are limited but molecular knowledge of the disease is significant. The INdividualized Screening trial of Innovative Glioblastoma Therapy (INSIGhT)[103] and the Adaptive Global Innovative Learning Environment for Glioblastoma (GBM-AGILE) were devised as multiarm platforms to support and inform drug development using

biomarkers that allow for accumulating trial data to identify possible responders.[104,105] As increasing numbers of outcome and pharmacodynamic biomarkers are developed for FTLD, similar approaches might be pursued.

7 | PERSONALIZED ENDPOINTS, DATA SHARING, AND NEW TECHNOLOGIES

Personalized clinical outcomes, in which the clinical outcome may vary between different patients in an effort to measure the most important and relevant signs, symptoms, functions, as well as the degree of severity of these impairments in each individual, are one approach to capturing heterogeneous changes in diseases caused by a common underlying pathology.[106,107] Such personalized outcomes are encouraged by the FDA's Patient-Focused Drug Development initiative.[108] Approaches to the development of personalized outcomes include the "most bothersome symptoms" approach,[106] goal attainment scaling (GAS),[109] and computer adaptive testing.[110] GAS is an example of how a quantitative approach to measuring individual outcomes can be developed within a structured method for documenting patient-centered problems and care.[111] The benefits of GAS are the improvement in stakeholder engagement and empowerment of the patient, caregiver, and clinician, as well as providing inherent clinical meaningfulness in capturing preferences.[112] It has been used successfully in AD clinical trials (ACADIE, VISTA) demonstrating GAS scores were more responsive than standard outcomes including the ADAS-Cog and the CIBIC+.[113–115] Other studies have subsequently determined that GAS can help dementia caregivers reach their own goals.[116] Other platforms such as the Hierarchy Model of Needs in Dementia have value in relating needs to individual goal-setting instruments for patients and caregivers.[117]

There is increased demand for broader data sharing by research funders and the recognition of a secure environment to store such data and make it available for analysis within the disease subset as well as externally to other diseases and potentially other data platforms. The limited capabilities of existing platforms that serve to disseminate preclinical and clinical data such as the National Alzheimer's Coordinating Center (NACC), Laboratory of Neuroimaging (LONI), and Database of Genotype and Phenotype (dbGAP), suggest that more fit-for-purpose platforms for multimodal data sharing for FTLD will be needed. Other drivers include the evolution of wearable devices and the use of mobile technology to record, store, and transmit user-produced data, creating a "digital phenotype" that can be uploaded and analyzed as part of clinical data collection, already in use in movement disorders research.[118–120] Database challenges include ensuring data privacy and security, gaining regulatory approval of remote tracking devices, extracting the maximal amount of information from the smallest number of devices and locations and validating outputs against existing standards, as well as providing sites that can not only store data but provide a cloud-based platform for data analysis with large data sets. The NIH "Accelerating Medicines Partnership" program for Parkinson's disease is a public-private partnership that seeks to address this challenge by creating a cloud-based resource that can store and analyze complex data sets for fluid biomarkers in patient and control populations. A similar effort could be developed with NIH for FTLD, or a focused precompetitive alliance of partners from industry, patient advocacy organizations, and philanthropy could accelerate this effort as has been done for Alzheimer disease through the Critical Path Institute (https://c-path.org/programs/cpad/).

Essential to the success of remote data collection and the creation of a shared database is concise informed consent to increase data and biospecimen access.[121] Critical to the success of any database is well-curated data and well-defined data standards[122,123] that can tease apart symptoms and signs that may be common across different diseases or subtypes. Such databases can transform clinical trials with high frequency, objective, and continuous data.[124] Developing a sustainable ecosystem that captures remotely tracked, continuous, biometric data will require a collaborative effort across many groups of stakeholders as demonstrated for AD with the Coalition to Prevent Alzheimer's Disease (CPAD) and Global Alzheimer's Association Interactive Network (GAAIN) databases, and Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT) for ALS.[125–127] Well-curated databases can speed the pace and reduce the cost of drug development by creating data standards that can aid in the evaluation of efficacy and safety of new therapies. They have the potential to be reviewed and qualified by the FDA as a "drug development tool", but to be successful will require buy-in from all stakeholders with relevant drug development pipelines.

8 | CONCLUSIONS AND FUTURE DIRECTIONS

Increasing numbers of clinical trials for FTLD are planned in the next few years. Particularly exciting are therapies targeting altered levels or mutant forms of products from the FTLD-causing genes, *C9orf72*, *GRN*, and *MAPT*. In addition, the successful enrollment of large clinical trials of anti-tau therapies in PSP is likely to enable new clinical trials of these therapies in sporadic FTLD syndromes with predicted underlying 4R tau pathology including nonfluent variant PPA and CBS.

Many challenges remain to finding effective therapies for FTLD. Further development of statistical and biomarker approaches to account for heterogeneity of phenotypes in both genetic and sporadic FTLD syndromes will be necessary to develop optimal clinical trial outcome measures. One potential solution is to develop personalized endpoints to measure treatment effects. These personalized endpoints may have increased clinical meaningfulness if approaches such a GAS are used as a basis for endpoint development.

Although a strong body of evidence now exists to support the use of blood or CSF NfL as a fluid biomarker to help define disease onset and severity of neurodegeneration, new biomarkers that can be deployed in asymptomatic FTLD mutation carriers or questionably symptomatic individuals with sporadic forms of FTLD will be necessary to allow inclusion of these individuals in clinical trials at the earliest stages of disease when new therapies are most likely to be effective. With

new FDA draft guidance for approval of drugs to prevent dementia in asymptomatic individuals who are at risk for disease, such biomarkers will be increasingly important in the future.

Novel clinical endpoints, possibly acquired through new wearable and other mobile technologies may further increase sensitivity and power to detect treatment effects, and might also be sensitive to early features of disease before the onset of overt clinical symptoms.[128] To make best use of these novel technologies, improved technological infrastructure and ironclad policies to ensure sharing of clinical and biomarker data and remaining biological specimens from completed clinical trials will also be necessary. Efforts to incorporate such policies into new treatment trials facilitated by or conducted within the North American ARTFL/LEFFTDS consortium and the European and Canadian GENFI project are an important first step to an improved publication and data sharing approach for FTLD clinical trials. Although there is much work to be carried out, the rapid pace of clinical therapeutic development for FTLD bodes well for the imminent development of effective therapies.

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